CYP2B6 Polymorphisms Challenge Generalized FDA Efavirenz Dosing Guidelines in Children < 3 yrs

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Poster # 903
CROI 2014
Boston, MA

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Updated Abstract

Background:
The FDA has published dosing recommendations for Efavirenz (EFV) in children less than 3 yrs of age based on safety, pharmacokinetic (PK), virologic and immunologic data from 3 open-label paediatric clinical trials. However, IMPAACT P1070 has found significant EFV PK variability in this age group due to a single genetic polymorphism in CYP2B6 516 (rs3745274); TT [Poor Metabolizers, **PM**] and GG or GT [Extensive Metabolizers**, EM**]. P1070 preliminary data suggest that FDA recommended dosages will result in a high proportion of EFV exposures outside of the therapeutic range.

Methods:
IMPAACT P1070 is an ongoing, prospective, phase I/II open-label 24 wk trial of EFV as opened capsules in HIV-infected children (Cohort 1) and HIV/TB co-infected children (Cohort 2, not reported), ages 3 to <36 months. In Version (V) 1, a high initial dose of EFV [~1600 mg x (weight in Kg/70)$^{0.7}$ rounded for weight band dosing] was used to produce a target AUC of 35-180 mcg*hr/mL, a systemic exposure shown to be effective and safe in older children and adults. Genotypic testing was performed in real-time from dried blood spots using a TaqMan probe assay and genotypic profile determined using allelic discrimination plots. 24 hour plasma PK data at week 2 were grouped by CYP2B6 516 genotype. Based on excessive exposures found in PMs in V1, dosages for PMs were reduced by 75% (~400 mg x (wt in Kg/70)$^{0.7}$) for V2. Expected AUC and C_{24} for FDA dosing were estimated from P1070 data: observed AUC or C_{24} X (FDA dose/study dose).

Results:
39 subjects have had 24 hr PK evaluation; 30 CYP2B6 EM and 9 CYP2B6 PM. Median apparent clearance (CL/F) was 0.41 L/h/kg in the EM subjects but only 0.09 L/h/kg in the PM subjects. The median C_{24} for EM/PM was 1.8/4.4 mcg/mL for P1070 V2 dosing and 0.9/8.5 mcg/mL for FDA dosing (target 1-4 mcg/mL). The AUC data for P1070 and FDA dosing are presented adjacent.

Conclusions:
Based on PK results from P1070, it appears that the FDA recommended doses of EFV will produce sub-therapeutic EFV AUCs in 33% of children <3 yrs who are extensive metabolizers (EM prevalence ~93% in Europeans and 80% of African Americans) and excessive AUCs in 67% of PM's. In contrast, CYP2B6 genotype directed dosing allowed for 83% of EM and 89% of PM children to achieve target EFV PK levels. Given the importance of achieving appropriate drug levels in this population, CYP2B6 genotyping prior to initiation of EFV will help optimize dosing in this age group.

Background

- EFV is a vital treatment option for HIV and HIV/TB co-infected infants/ young children but optimal dosing data are lacking.
- Sub-therapeutic drug levels and wide variations in the plasma concentrations have been described among children using liquid suspensions (1;2).
- The FDA recently published dosage guidelines for children less than three years of age, based on weight, using data from earlier open label clinical trials.
- IMPAACT P1070 has revealed marked inter-patient PK variability due to cytochrome 2B6 (CYP2B6 516) genotypic polymorphisms (2;3).
- Based on these data, we predict FDA recommended dosages will result in PK exposures outside the therapeutic range in a significant proportion of children.

Methods

- IMPAACT P1070 is an ongoing, prospective, phase I/II open-label 24 wk trial of EFV as opened capsules in HIV-infected children (Cohort 1) and HIV/TB co-infected children (Cohort 2, not reported), ages 3 to <36 months.
- Using recently published dosing guidelines, the predicted AUC and C_{24} for FDA dosing were estimated from P1070 data using the following : observed AUC or C_{24} X (FDA dose/study dose)
- Following this, the expected proportion of infants and young children achieving a steady state AUC of *35-180* mcg*hr/mL and C_{24} of 1-4mcg/mL was calculated.
- Modeled subjects falling within these ranges were assumed likely to have achieved therapeutic drug levels.

P1070 Dosing

- In Version (V) 1, a high initial dose of EFV [~1600 mg x (weight in Kg/70)$^{0.7}$ rounded for weight band dosing] was given to produce a target AUC of 35-180 mcg*hr/mL.
- In V2, dosages were based on 'real time' genotyping and were reduced by 75% for PM's (V2 approved in December, 2011).
- Individual dose adjustments were made if PK results fell outside of therapeutic range.

FDA Dosing (3,4)

- Based on population PK modeling using both paediatric and adult data from PACTG 382, PACTG 1021, BMS A1266922 and A1266059
- Simulations of steady state EFV exposures were performed

Weight (kg)	P1070 V1 (mg)	P1070 EM V2 (mg)	FDA (mg)	P1070 PM V2 (mg)
3-3.5	200	200	-	50
3.5-5	200	200	100	50
5-7	300	300	150	50
7-7.5	400	400	150	100
7.5-10	400	400	200	100
10-14	400	400	200	100
14-15	500	500	200	150
15-17	500	500	250	150

Results

Baseline Demographics

- N=39 Male: 59%
- Race: Black=69%; Asian=28%; Unknown=3%
- CYP2B6 genotype: PM=77% (30/39); EM=23% (9/39)

	Median	25th Percentile	75th Percentile
AGE (months)	22	14	28
CD4 (%)	20.8	15	26.1
CD4 (cells/ mm^3)	1266	1005	1647
HIV RNA (log 10)	5.76	5.29	5.88

Pharmacokinetics (P1070 PK data and Predicted FDA Exposures)

EFAVIRENZ Area Under the Curve (AUC)

EM (CYP2B6 516 GG/GT) n=30	Median AUC (mcg*h/mL) [95%CI]	# w/ Estimated Plasma AUC <35 mcg*h/mL	# w/ Estimated Plasma AUC in [35-180] mcg*h/mL	#w/ Estimated Plasma AUC >180 mcg*h/mL
P1070 V1 & V2 dosing*	105.6 [58.5,129.6]	4 (13.3%)	25 (83.3%)	1 (3.3%)
FDA dosing **	52.8 [29.4,64.8]	10 (33.3%)	19 (63.3%)	1 (3.3%)
PM (CYP2B6 516 TT) n=9				
P1070 V2 dosing**	122.6 [93.2,162.6]	0 (0%)	8 (88.9%)	1 (11.1%)
FDA dosing **	245.1 [162.2,325.1]	0 (0%)	3 (33.3%)	6 (66.7%)

* observed values ** predicted values

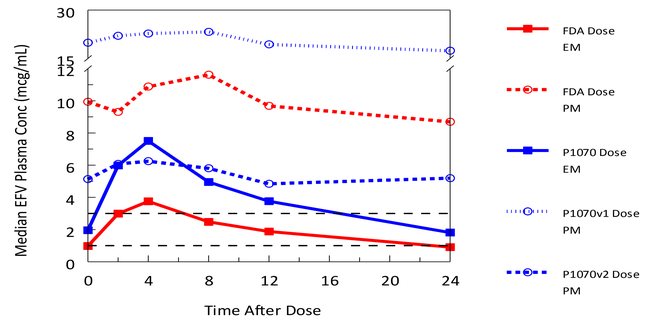
EFAVIRENZ C 24

EM (CYP2B6 516 GG/GT) *n=30*	Median C24 (mcg/mL) [95%CI]	# w/ Estimated Plasma C24 *<1* mcg/mL	# w/ Estimated Plasma *C24 in [1-4]* mcg/mL	#w/ Estimated Plasma C24 >4 mcg/mL
P1070 V1 & V2 dosing*	1.8 [1.1, 3.0]	8 (26.7%)	17 (56.7%)	5 (16.7%)
FDA dosing **	0.9 [0.5, 1.5]	16 (53.3%)	13 (43.3%)	1 (3.3%)
PM (CYP2B6 516 TT) n=9				
P1070 V2 dosing**	4.4 [3.1, 6.1]	0 (0%)	3 (33.3%)	6 (66.7%)
FDA dosing **	8.5 [5.1, 12.1]	0 (0%)	1 (11.1%)	8 (88.9%)

*observed values **predicted values

PK Outcomes

Figure 1: P1070 24 Hour PK at Week 2



Safety Outcomes

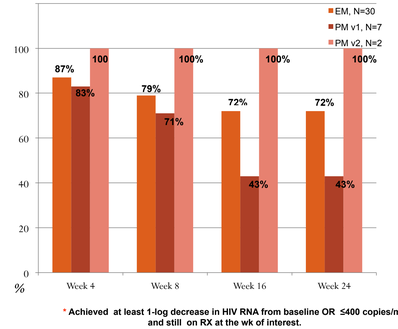
Early Treatment Discontinuations

- 26 subjects *completed* treatment
- 3 *discontinued* due to protocol defined *toxicity (**PM**:Gr4 ANC-poss Rx rel; **EM**:Gr3 Neurotox/Lethargic-poss Rx rel; Gr4 Lipase-not rel)*
- 4 *were withdrawn for non Rx rel reasons*,
- 5 *discontinued* due to failure to meet PK targets.
- Subjects discontinuing prior to 24 weeks (off treatment range: 4-19 wks) had median log drop in HIV RNA of >2.7 from baseline at discontinuation

At least 'possibly RX related' events:
N=4 PM/Mutant (all associated with HIGH AUC)
(1) Gr2 SGPT at wk 24
(1) Gr4 ANC at wk 4-7 – discontinued RX
(1) Gr3 Hemoglobin, Gr2 Pallor at wk 5
(1) Neurologic Toxicity: Gr1 Drowsiness, 1day after RX
N=6 EM/Non-Mutant
(1) Gr2 Bicarbonate at wk 12 (met target AUC)
(2) Gr3 ANC at wk 8 (high AUC); wk 12-16 (met target AUC)
(2) Gr2 Drug rash at wk 1 (low AUC); wk 2 (met target AUC)
(1) Neurologic Toxicity: Gr3 Lethargy on the 1st day of RX with Gr2 Febrile Seizures at wk 1 (met target AUC) – discontinued RX

Virological Outcomes

Figure 2: Virological Response (Intention to treat analysis)



* Achieved at least 1-log decrease in HIV RNA from baseline OR ≤400 copies/ml and still on RX at the wk of interest.

Discussion

Based on PK results from P1070, it appears that the FDA recommended doses of EFV will produce sub-therapeutic EFV AUCs in 33% of children <3 yrs who are extensive metabolizers (EM prevalence ~93% in Europeans and 80% of African Americans (5)) and excessive AUCs in 67% of PM's. In contrast, CYP2B6 genotype directed dosing allowed for 83% of EM and 89% of PM children to achieve target EFV PK levels.

Conclusions

Significant inter-subject PK variations, largely dependent on CYP 2B6 genotype, challenge the use of generalized recommended EFV dosages for young children. Genotype directed dosing at P1070 doses results in most subjects achieving targets (with favorable safety and virologic outcomes) and appears to out-perform other suggested dosing approaches.

References:
(1) Ren Y, Nuttall J, Egbers C et al. High prevalence of sub-therapeutic plasma concentrations of efavirenz in children. J Acquir Immune Defic Syndr 2007; 45(2): 133-136.
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(4) U.S Food and Drug Administration. Sustive (efavirenz) pediatric patients labeling update. May 02, 2013. http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/HIVandAIDSActivities/ucm350744.htm

The study team would like to thank the 1070 participants and families for their participation and Aurobindo Pharma Limited for donating the Efavirenz.